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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,489	03/01/2004	Serge Carillo	ST94037B	9027

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EXAMINER
LONG, SCOTT

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,489	CARILLO ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-8 are pending. Claims 1-8 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 1 March 2004 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The information disclosure statement filed 3/1/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 *because the applicant has submitted PTO-892 forms from parental cases. Applicant should submit a new listing that complies with the format requirements in 37 CFR 1.98(a)(1).*

MPEP 609.02 [R-5] Information Disclosure Statements in Continued Examinations or Continuation Applications, Divisional Applications, or Continuation-in-Part Applications Filed Under 37 CFR 1.53(b)

The examiner will consider information which has been considered by the Office in a parent application when examining: (A) a continuation application filed under 37 CFR 1.53(b), (B) a divisional application filed under 37 CFR 1.53(b), or (C) a continuation-in-part application filed under 37 CFR 1.53(b). A listing of the information need not be resubmitted in the continuing application unless the applicant desires the information to be printed on the patent. If resubmitting a listing of the information, **applicant should submit a new listing that complies with the format requirements in 37 CFR 1.98(a)(1).** Applicants are strongly discouraged from submitting a list that includes copies of PTO/SB/08 ** or PTO-892 forms from other applications. A completed PTO/SB/08 ** form from another application may already have initials of an examiner and the application number of another application. This information will likely confuse the record. Furthermore, when the spaces provided on the form have initials of an examiner, there are no spaces available next to the documents listed for the examiner of the subsequent application to provide his or her initials, and the previously relevant initials may be erroneously construed as being applied for the current application.

Priority

This application claims benefit as DIV of 09/405,920 (filed 09/24/1999 ABN) which is a CON of 08/737,953 (filed 11/27/1996 ABN) which is a 371 of PCT/FR95/00670 (filed 05/22/1995). The application also claims benefit from foreign application, FRANCE FR94/06583 (filed 05/31/1994). The instant application has been granted the benefit date, 22 May 1995, from the application PCT/FR95/00670.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 and 5-7 recites the limitation "the inhibitor." It is not clear which inhibitor is referred to, since claim 1 recites two different inhibitors, “an inhibitor of p53” and “an inhibitor or calpain protease activity.” There is insufficient antecedent basis for this limitation in the claim. In order to further prosecution, examiner will interpret the limitation, “the inhibitor” as “the inhibitor of calpain protease activity.” Therefore, claim 2, for example, will be interpreted as “the method of claim 1, wherein the inhibitor of calpain protease activity is a calpastatin.”

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 USC § 112, p 1 "Written Description" Requirement;* (Federal Register/Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 5 and 7 are broadly drawn, such that they applies to a genus of calpastatin fragments. However, the working examples provided in the instant application do not demonstrate any individual species of calpastatin fragments. The specification indicates, "Various fragments or derivatives of calpastatin can be used within the framework of the present invention. Such 5 fragments or derivatives may be any molecule obtained from the sequence SEQ ID No. 1 by modification(s) of a genetic and/or chemical nature, preserving the capacity to inhibit, at least in part, the activity of a calpain. Modification of a genetic and/or chemical nature is understood to mean any mutation, deletion, substitution, addition and/or modification of one or more nucleotides" (page 6, lines 2-12). The specification does not describe particular structure that are required for calpastatin functionality.

The Revised Interim Guideline for Examination of Patent Applications under 35 USC § 112, p1 "Written Description" Requirement (Federal Register/ Vol 66. No 4, Friday January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (column 2, page 71436, emphasis added).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize the [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Considering the potentially large numbers of polypeptides and polynucleotides encompassed by these claims, the disclosure is not sufficient to show that a skilled

artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Rambsy et al. Electrophoresis. 1994 Feb;15(2):265-77.

Claim 1 is directed to a method for detecting an inhibitor of p53 protein degradation comprising providing a cell extract containing one or more p53 proteins and one or more proteases, administering an inhibitor of calpain protease activity, and measuring p53 protein and p53 protein fragments. Rambsy et al. teach, "two-dimensional (2-D) gel electrophoresis...used...to assess...protein...degradation" (page 265, Abstract). Rambsy et al. teach, "extraction of isolated hepatocytes" (page 268, col.1, Results and Discussion). Rambsy et al. teach "distribution of proteins in 2-D gels" including p53 protein (page 275). Rambsy et al. teach, use of EDTA which is "an effective inhibitor of the calcium-activated proteases, calpains I and II. These proteases,

along with their endogenous inhibitor, calpastatin, are predominantly cytosolic proteins." (page 271, col.1, 2nd parag.).

Claim 2 is directed to the method of claim 1, wherein the inhibitor is a calpastatin. Rambsy et al. teach the endogenous inhibitor of calpain is calpastatin (page 271, col.1, 2nd parag.).

Claim 8 is directed to the method of claim 1, wherein measuring the p53 protein and p53 protein fragments is performed using gel electrophoresis. Rambsy et al. teach "distribution of proteins in 2-D gels" including p53 protein (page 275).

Accordingly, Rambsy et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rambsy et al. *Electrophoresis*. 1994 Feb;15(2):265-77. in view of Asada et al. *J. Enzym. Inhib*. 1989 3 (1), 49-56.

Claim 3 is directed to the method of claim 2, wherein the calpastatin is encoded by one of SEQ ID NO: 1-3.

Claim 4 is directed to method of claim 1, wherein the cell extract is derived from a tumor cell.

Claim 6 is a method of claim 4, wherein the inhibitor is a calpastatin.

Claims 5 and 7 are directed to the methods of claims 1 and 4, respectively, wherein the inhibitor is a fragment of calpastatin.

The teachings of Rambsy et al. are described above in the 35 USC 102 section. In addition, Rambsy et al. teach that their method "is applicable to use with limited amounts of biomaterial and with other cell types or culture systems" (page 276, Conclusions), inferring that it is obvious to use their system with any cell extract, including tumor cell extracts.

Rambsy et al. does not specifically teach the limitations of claims 2, directed to the particular SEQ ID NO:1-3, and limitations of claims directed to tumor cell extracts and the limitations of claims directed to fragments of calpastatin.

Asada et al teach an isolated cDNA of human calpastatin, an inhibitor protein specific for calpain. The sequence taught by Asada et al. is 100% identical to SEQ ID NO:3 of the instant application.

In addition, the instant specification states, "Calpastatin is a known inhibitor of the calpains. Its sequence has been described in the prior art (SEQ ID No. 1)." (page 5, lines 22-24).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute tumor cell extracts for hepatocyte cell extracts in the gel electrophoresis method of Rambsy et al. and further to substitute any of a variety of calpastatins to inhibit proteases in the cell extract.

The person of ordinary skill in the art would have been motivated to substitute one known, equivalent element for another to obtain predictable results. The claimed methods would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant case, it would have been obvious to substitute any calpastatin (for example, the calpastatin taught by Asada et al. or as described in the prior art, SEQ ID NO:1) for that taught by Rambsy et al. because the functionality of various calpastatins is the same (i.e. – inhibitors of protease Calpain). Furthermore, Rambsy et al. teach that their method "is applicable to use with limited amounts of biomaterial and with other cell types or culture systems" (page 276, Conclusions), so the particular type of cell extract is not important and any cell type can be substituted in the method of Rambsy et al. As far as the claim limitations regarding using fragments

of calpastatin, the instant application clearly indicates the obviousness of substituting functional equivalents of calpastatin comprising fragments for those used in any method that requires inhibitors of calpain, "Various fragments or derivatives of calpastatin can be.used within the framework of the present invention. Such 5 fragments or derivatives may be any molecule obtained from the sequence SEQ ID No. 1 by modification(s) of a genetic and/or chemical nature, preserving the capacity to inhibit, at least in part, the activity of a calpain. Modification of a genetic and/or chemical nature is understood.to mean any mutation, deletion, substitution, addition and/or modification of one or more nucleotides " (page 6, lines 2-11). No particular structure of the calpastatin fragments is taught, so any substitute would be obvious.

Therefore the method as taught by Rambsy et al. in view of Asada et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JLE